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Involvement of Opioid μ1 Receptors in Morphine-Induced Conditioned Place Preference In Rats

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PIEPPONEN, T. P., T. KIVASTIK, J. KATAJAMÄKI, A. ZHARKOVSKY AND L. AHTEE. *Involvement of opioid μ1 receptors in morphine-induced conditioned place preference in rats.* PHARMACOL BIOCHEM BEHAV **58**(1) 275–279, 1997.—The main purpose of this study was to evaluate the role of μ1-opioid receptors in morphine reward. Therefore, we studied the ability of a μ1-selective antagonist, naloxonazine [15 mg/kg intraperitoneally (IP)], to antagonize the conditioned place preference (CPP) induced by morphine [3 mg/kg subcutaneously (SC)]. In addition, effects of naloxonazine on morphine-induced catalepsy (15 mg/kg), analgesia (3 mg/kg), and hyperthermia (3 mg/kg) were studied. For comparison, the effects of a nonselective opioid receptor antagonist, naltrexone (2.5 mg/kg SC), and a selective δ-opioid receptor antagonist, naltrindole (2 mg/kg IP), on CPP induced by morphine were investigated. Morphine-induced CPP was clearly antagonized by pretreatment with naloxonazine and naltrexone (12 h and 20 min prior to morphine, respectively) but not by naltrindole (15 min before morphine). Naloxonazine also antagonized morphine-induced catalepsy and analgesia but not morphine-induced hyperthermia. Naltrindole did not modify morphine-induced catalepsy. These results suggest an active role for μ1-opioid receptors in morphine reward, whereas morphine-induced hyperthermia does not appear to be mediated by μ1-opioid receptors. Furthermore, δ-opioid receptors seem to be without significance in morphine-induced reward. © 1997 Elsevier Science Inc.

Naltrexone Naloxonazine Naltrindole Conditioned place preference Catalepsy Analgesia Hyperthermia Opioid receptors

THE μ-OPIOID receptors are regarded as the primary site of action for the rewarding effects of opioids (6). Binding studies have identified two subtypes of μ-opioid receptors: one, μ1, with a high affinity for both morphine and enkephalins, and one, μ2, with a lower affinity that, however, binds morphine far more potently than it binds the enkephalins (42). The pharmacological roles of these subtypes have mainly been characterized with the μ1-selective antagonist naloxonazine (29). Naloxonazine antagonizes a variety of morphine's actions, including analgesia, without affecting a number of others, such as respiratory depression and increased striatal dopamine turnover (29). It is not known how these subtypes are involved in the rewarding effects of μ-receptor activating drugs in rats. Therefore, we have studied whether μ1-receptors are involved in the morphine reward by investigating the effect of naloxonazine on morphine-induced conditioned place preference (CPP). To evaluate the effectiveness and selectivity of the dose of naloxonazine used, we also measured its effects on morphine-induced antinociception and hyperthermia. In smaller doses, systemically given morphine elicits antinociception in rats predominantly supraspinally through μ1-opioid receptors, whereas in larger doses, μ2-opioid receptors become predominant (35). Morphine-induced hyperthermia is readily antagonized by naloxone (3), which blocks all subtypes of opioid receptors. The possible role of μ1- and μ2-opioid receptors in hyperthermia has not been investigated prior to this study.

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For comparison, we investigated the effects of the nonselective opioid antagonist naltrexone and the selective δ-opioid antagonist naltrindole on morphine-induced CPP. Besides the μ-receptor, morphine has some affinity for δ-opioid receptors (4), which have been shown to mediate rewarding effects as well (12,33,36). There is also evidence that, in mice, blockade of δ-opioid receptors prevents the rewarding effects of morphine (39). Therefore, to validate the effectiveness and selectivity of the dose used, we also wanted to clarify whether δ-opioid receptors are involved in the acute rewarding effects of morphine in rats.

In rats, large doses of opioids elicit catalepsy (1), a state of immobilization that is regarded as a mixture of muscle rigidity and akinesia. Opioid-induced catalepsy has been shown to be mediated by μ-opioid receptors, especially μ1-receptors (16,27), whereas the activation of δ-receptors has been shown to mediate only stimulatory effects, e.g., locomotor activation and stereotypies (18,24). Therefore, to validate the effectiveness and selectivity of the doses used, we also studied the effects of naloxonazine and naltrindole on morphine-induced catalepsy.

METHODS

Animals

Male Wistar rats weighing 250–400 g were used. The rats were housed in groups of four to six under a 12 L:12 D cycle (lights on at 0600 h) with food and water ad lib. The experiments were carried out during the light phase of the cycle.

Catalepsy

Catalepsy was measured every 30 min for 150 min after administration of morphine [15 mg/kg subcutaneously (SC)]. Four tests were used: a) both front limbs of the rat were gently placed onto a 3-cm-high horizontal bar; b) both front limbs were gently placed onto a 9-cm-high bar; c) the front and hind limbs were placed onto parallel horizontal bars with a 6-cm distance between them; and d) the rat was placed on a metal grid positioned at an angle of 45°. Each test was scored from 0 to 2: a score of 1 was given if the animal remained immobile for 10 s, and a score of 2 was given if the animal remained immobile for 20 s or more. The four tests were repeated five times during the 2.5-h experiments; the scores were summed and taken as a measure of the catalepsy (maximum sum was 40). Naloxonazine [15 mg/kg intraperitoneally (IP)] and naltrindole (2 mg/kg IP) were given 24 h and 15 min before morphine, respectively.

Analgesia Testing and Rectal Temperature Measurement

The pain sensitivity of rats was tested with hot plate (43). The animals were gently placed on a 55°C copper plate, and the time to onset of paw-licking movements was taken as the latency period. The cut-off time was 30 s. Naloxonazine (15 mg/kg IP) was given 12 h prior to morphine (3 mg/kg SC). Latencies were measured 30 and 60 min after administration of morphine. Antinociceptive effect was calculated as a percentage of maximum possible effect (%MPE):

$$\%\text{MPE} = \frac{\text{LTT} - \text{LTC}}{\text{CT} - \text{LTC}} \times 100,$$

where LTT = latency time of treated animals, LTC = latency before treatment, and CT = cut-off time.

Rectal temperature was measured immediately before the hot-plate test by an electrical thermometer (Ellab, Copenhagen, Denmark) using a 4-cm-long rectal probe. The animals were unrestrained during measurements.

Conditioned Place Preference

CPP was studied in an apparatus consisting of two square-based compartments (30 × 30 × 40 cm high), one with white and the other with dark gray walls and floor. The compartments were separated by a guillotine door and covered with a transparent Plexiglas ceiling. The apparatus was placed into a dimly lit room with masking noise provided by a ventilation fan.

Experimental Procedure

Before starting the experiments, the rats were acclimatised to experimenter contact for 3 days by handling and weighing them. The procedure was similar to that described previously (13).

Each experiment consisted of three phases:

1. Preconditioning: For 3 days (days 1, 2, and 3) rats were given free access to both compartments of the apparatus for 15 min (900 s) each day. On day 3, the time spent by the rats in each compartment was recorded and these values served as a baseline.
2. Conditioning was conducted for 4 days (days 4, 5, 6, and 7) and included two sessions each day. Rats were given SC morphine (3 mg/kg) or saline (controls) immediately before placing them in the nonpreferred compartment for 60 min. After an interval of 4 h, all of the rats were given saline SC and placed in the preferred compartment for 60 min. The order of morphine and saline presentation paired with the given environment was balanced across treatment

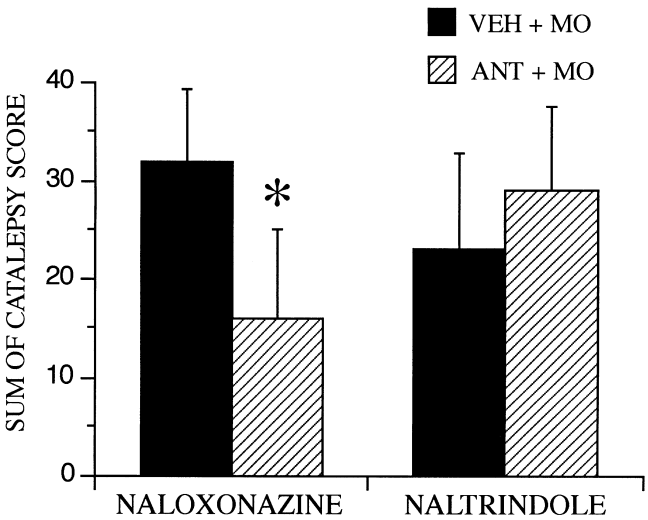

FIG. 1. Effects of opioid antagonists naloxonazine (15 mg/kg IP, 12 h before morphine) and naltrindole (2 mg/kg IP, 15 min before morphine) on catalepsy induced by morphine (15 mg/kg SC). The control rats received vehicle 12 h or 15 min before morphine, respectively. The columns show the summed catalepsy scores of five measurements at 30-min intervals after morphine administration. Median values ± 95% confidence limits are given (n = 6–9). VEH, vehicle; MO, morphine; ANT, antagonist. *$p < 0.05$ (Mann–Whitney U-test).

TABLE 1

EFFECT OF NALOXONAZINE PRETREATMENT ON MORPHINE-INDUCED ANTINOCICEPTION AND HYPERTHERMIA

	Time after Morphine Administration (min)		
Pretreatment	0	30	60
		Latency	
Vehicle	8.4 ± 2.9	16.2 ± 3.2*	9.4 ± 1.4
Naloxonazine	12.8 ± 3.3	12.3 ± 3.0	10.0 ± 2.9
		%MPE	
Vehicle		31.6 ± 15.1	0.5 ± 14.4
Naloxonazine		−12.2 ± 26.1†	−2.6 ± 23.2
		T_{rect} (°C)	
Vehicle	38.0 ± 0.1	38.6 ± 0.2*	38.7 ± 0.2**
Naloxonazine	38.3 ± 0.1	38.9 ± 0.1**	38.9 ± 0.2*

Naloxonazine (15 mg/kg IP) was given 12 h prior to morphine (3 mg/kg SC). Antinociception was measured by estimating the latency (s), and mean percentages of maximum possible effect (%MPE) were calculated. Rectal temperatures [T_{rect} (°C)] were measured from the same animals immediately before placing them on the hot plate. The median values ± 95% confidence limits (latency and %MPE) or the mean values 6 SE [T_{rect} (°C)] of seven or eight animals are given. *$p <$ 0.05 and **$p < 0.01$ vs. corresponding value at 0 min, Wilcoxon signed-rank test (latency and %MPE) or Student's paired two-tailed *t*-test (T_{rect}). †$p < 0.05$ vs. vehicle pretreatment, Mann–Whitney *U*-test.

groups. Naltrexone (2.5 mg/kg SC), naloxonazine (15 mg/kg IP), and naltrindole (2 mg/kg IP) were given 20 min, 12 h, and 15 min prior to morphine, respectively.

3. Postconditioning: On day 8, the rats had free choice in the apparatus for 15 min (no drugs were administered), and the time spent in each compartment was recorded.

Drugs

Naloxonazine (RBI, Natick, MO, USA) was suspended in 2.5% Tween® 80 solution. Naltrindole HCl (RBI, Natick, MO, USA) was dissolved in a 22.5% (w/v) solution of 2-hydroxypropyl-β-cyclodextrin. Morphine HCl (Ph. Eur., 2nd ed.) and naltrexone HCl (Sigma, MO, USA) were dissolved in saline. Drugs were administered at a dose of 2 ml/kg (doses except for naltrindole given as base).

Statistics

The data obtained in CPP experiments were subjected to two-way analysis of covariance (ANCOVA), the baseline serving as a covariate. For multiple comparisons, the Tukey compromise post hoc test was used. Data from hot-plate tests were analyzed with either the Wilcoxon signed-rank test (effects of acute drug) or the Mann–Whitney *U*-test (effects of pretreatment). Catalepsy scores were compared with the Mann–Whitney *U*-test. Rectal temperatures were compared with a paired *t*-test (two-tailed).

RESULTS

Catalepsy, Antinociception, and Rectal Temperature

Morphine (15 mg/kg SC) produced a marked cataleptic effect that lasted for about 120 min. This catalepsy was signifi-

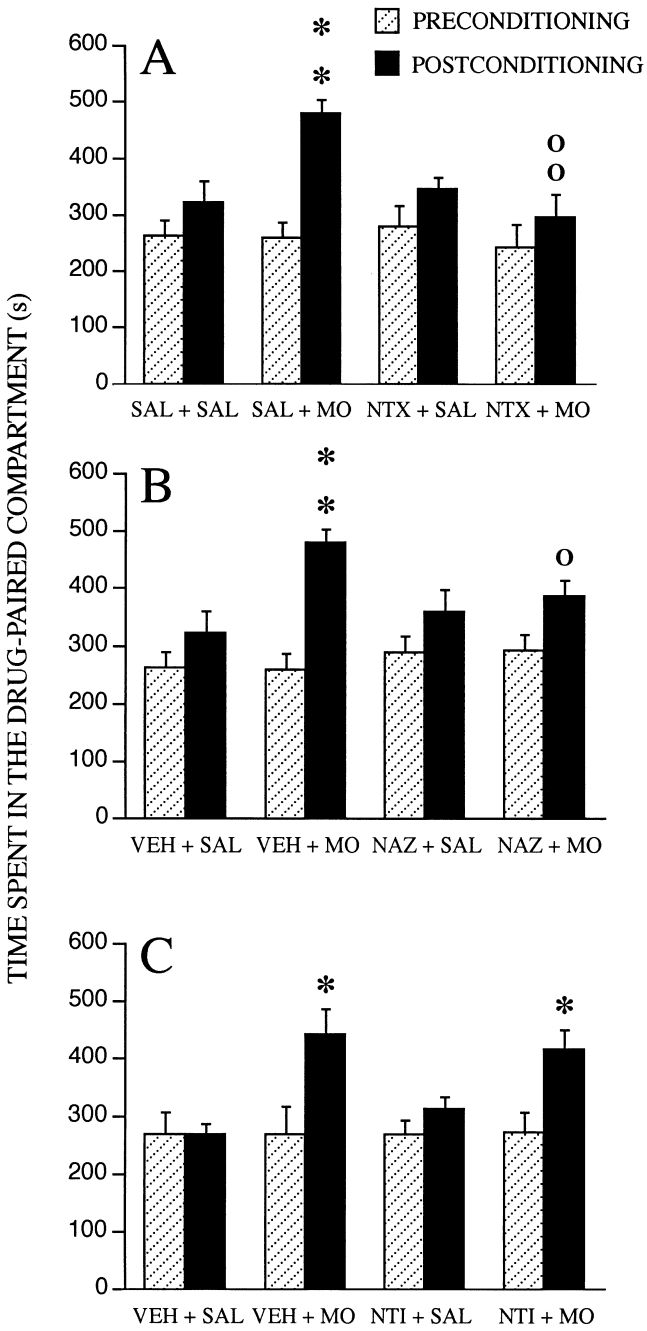

FIG. 2. Effects of opioid antagonists naltrexone (NTX, 2.5 mg/kg SC, panel A), naloxonazine (NAZ, 15 mg/kg IP, panel B), and naltrindole (NTI, 2 mg/kg IP, panel C) on conditioned place preference induced by morphine (3 mg/kg SC). The antagonists were administered 20 min, 12 h, and 15 min before morphine, respectively. The control rats received saline (SAL) or vehicle (VEH). The columns show the times (means ± SE) rats (n = 7–18) spent in the initially nonpreferred (white) compartment during preconditioning (shaded columns) and postconditioning (filled columns). *$p < 0.05$ and **$p < 0.01$ vs. control group. °$p < 0.05$ and °°$p < 0.01$ vs. morphine group (Tukey compromise test).

cantly antagonized by naloxonazine ($U = 13.5$, $p = 0.017$ as compared with vehicle pretreatment, Mann–Whitney U-test) but not by naltrindole (Fig. 1).

Naloxonazine clearly antagonized morphine-induced antinociception (Table 1). Naloxonazine itself tended to increase the baseline latency ($U = 16$, $p = 0.0924$, Mann–Whitney U-test).

Morphine induced a significant hyperthermic effect at 30 and 60 min after its administration. Naloxonazine did not alter this effect of morphine (Table 1).

Place Preference Conditioning

In all the experiments, rats treated with morphine showed significant preference [$F(1, 47) = 5.18$, $p = 0.0276$; $F(1, 49) = 12.56$, $p = 0.0009$; and $F(1, 28) = 23.66$, $p < 0.0001$ for the experiments with naltrexone, naloxonazine, and naltrindole, respectively] for the drug-associated compartment (Fig. 2). This preference was clearly antagonized by both the nonselective opioid antagonist naltrexone and the μ1-receptor-selective antagonist naloxonazine [$F(1, 47) = 8.32$, $p = 0.0059$ and $F(1, 49) = 3.49$, $p = 0.0678$; for the interactions with morphine: $F(1, 47) = 10.649$, $p = 0.002$ and $F(1, 49) = 6.88$, $p = 0.012$, respectively]. The δ-selective antagonist naltrindole did not interact with the effect of morphine [$F(1, 28) = 0.09$, $p = 0.76$; for the interaction with morphine: $F(1, 28) = 1.57$, $p = 0.22$]. None of the antagonists alone significantly affected the CPP.

DISCUSSION

The CPP paradigm has proven to be a valuable tool in the investigation of rewarding (or aversive) properties of drugs [for reviews, see (10,11)]. In this method, the subjects learn to associate the primary rewarding stimulus with the environmental stimulus or, in other words, the environmental secondary stimulus (place) acquires rewarding properties through the conditioning. In our experiments, the morphine-induced place preference was significantly antagonized by the nonselective opioid antagonist naltrexone, as well as by the μ1-opioid receptor selective antagonist naloxonazine. Thus, our results indicate that μ1-opioid receptors are critically involved in the rewarding properties of morphine. This is not surprising, because μ1-opioid receptors have been shown to be involved in natural rewards like feeding (19,21,34), drinking (19,34), and maternal behaviour (20). Naloxonazine has also been shown to partially antagonize the increase of locomotor activity induced by the selective μ-opioid agonist DAGO (15). Further, rats readily orally self-administer etonitazene (2), a potent opioid that has recently been shown to be a rather selective agonist for μ1-opioid receptor (25). Etonitazene also induces CPP (31). Thus, it seems likely that although μ1-selective opioid analgesics may lack some undesirable effects like respiratory depression and inhibition of gastrointestinal transit, they would not be without rewarding effects.

Naloxonazine is an azine derivative of naloxone, and in binding studies the behaviour of reversibly bound naloxonazine closely resembles that of naloxone, i.e., it binds to all types of opioid receptors (9). Only irreversible binding of naloxonazine has been shown to be μ1-selective, and under in vivo conditions the best μ1-selectivity with this drug is reached when it is given about 24 h before an agonist (17). In our experiments, for methodological reasons (to prevent overlapping with conditioning sessions), naloxonazine was given 12 h before morphine (except in the catalepsy experiment, where it was given 24 h before morphine). It may be argued that at this time (12 h after administration), naloxonazine may have affinity for other opioid receptors besides the μ1-opioid receptors. However, the fact that naloxonazine was not able to antagonize morphine-induced hyperthermia, an effect that is readily antagonized by the nonselective antagonist naloxone [for an extensive review, see (3)], strongly indicates its clear selectivity for the putative μ1-site using this means of administration. Furthermore, our finding suggests that morphine-induced hyperthermia is not mediated by μ1-receptors.

In contrast to our findings in rats, in mice the blockade of μ1-receptors by naloxonazine did not affect morphine-induced CPP (37). This may be because mice differ from rats in many respects, such as the distribution and proportion of opioid receptors in various areas of the brain (7,8,22,41). Rats and mice also differ in their behavioural response to morphine; large doses of morphine induce catalepsy in rats (μ1-effect) but locomotor activation in mice (14,30). Differences in opioid receptor-mediated functions also occur between different strains of rats: e.g., etonitazene, a possible μ1-opioid receptor selective agonist, serves as a reinforcer in one rat line but not in another (38).

Recent reports have emphasized the role of δ-receptors in the rewarding properties of cocaine (23). Also, δ-receptors have been proposed to mediate rewarding effects produced by intra-accumbal morphine administration (32). Furthermore, δ-opioid antagonists were shown to abolish the morphine-induced place preference in mice (39). Although the affinity of morphine to δ-receptors is relatively low as compared with μ-receptors (4), δ-receptors could mediate part of rewarding effects of morphine in rats as well. Our results, however, do not support this idea, because naltrindole was without effect on morphine-induced CPP. Neither did intracerebral administration of δ-antagonist, ICI 174,864, modify the CPP induced by intracerebroventricular morphine (33). Furthermore, naltrindole affected heroin self-administration only at doses [10 and 15 mg/kg (26)] that were 10–1000-fold larger than the ones needed to antagonize the antinociception induced by the selective δ-agonists DPDPE or DSLET (5). Because naltrindole blocks both putative subtypes (δ1 and δ2) of δ-receptors (28,40), it seems unlikely that δ-opioid receptors are involved in the rewarding effects of morphine in rats.

In conclusion, our results indicate a distinct role for μ1-opioid receptors in the rewarding effects of morphine in rats; δ-opioid receptors appear to be without significance in this respect, as well as in the mediation of morphine-induced catalepsy. Furthermore, our results confirm that μ1-opioid receptors play an active role in the mediation of morphine-induced antinociception and catalepsy. In contrast, μ1-opioid receptors do not seem to be involved in morphine-induced hyperthermia.

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